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ISSUE HIGHLIGHTS

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Luck o' the Irish!

New Drug Interactions and Adverse Drug Reactions with Cisapride

Cisapride (Propulsid® - Janssen Pharmaceutica) has been reported to cause QT prolongation and ventricular arrhythmias, including torsades de pointes, in patients receiving multiple medications who were chronically ill or had other potential risk factors for arrhythmias. According to Janssen, the rate of serious ventricular arrhythmias in patients treated with cisapride has been about 1 per 120,000 patients and about 1 per 400,000 patient-months.

According to Janssen Pharmaceutica, two reports of ventricular arrhythmias, including torsades de pointes, associated with QT prolongation occurred in patients taking cisapride and ketoconazole (Nizoral® - Janssen Pharmaceutica). Oral ketoconazole potently inhibits the cytochrome P450 enzyme system (3A4) responsible for cisapride metabolism resulting in markedly elevated cisapride plasma concentrations and prolonged QT intervals.

Additionally, due to potent in vitro inhibition of this hepatic enzyme system, itraconazole (Sporanox® - Janssen), miconazole IV (Monistat™ - Janssen), and troleandomycin (TAO® - Roerig) are also expected to markedly raise cisapride levels. According to C. DeLoria, Pharm.D. at Janssen Pharmaceutica, fluconazole (Diflucan® - Roerig) and erythromycin were considered weak inhibitors of this hepatic enzyme system in vitro (February 23, 1995).

Because of the potential occurrence of serious ventricular arrhythmias, including torsades de pointes, the concomitant use of cisapride and ketoconazole, itraconazole, miconazole IV, or troleandomycin is contraindicated. The package insert for cisapride has been changed to include this new information. Janssen Pharmaceutica will change the package inserts for ketoconazole, itraconazole, and miconazole IV as well to reflect this information.

Request for Asthma Information

The PEC is starting to review data and develop analyses for the treatment of pediatric and adult asthma, and is interested in obtaining information from military treatment facilities. If your facility has a specific treatment protocol for asthma management, results of drug use evaluations of asthma therapy, data from asthma outcomes studies, innovative patient education programs or monitoring tools, or any other information related to the treatment of asthma that you are willing to share, the PEC would like this information to include in their analyses.

IN CURRENT LITERATURE.....

Measuring and Improving Physician Compliance with Clinical Practice Guidelines

The last issue of the PEC Update (95-05) included an article describing the benefits and risks associated with practice guidelines. Many factors may contribute to the reservations clinicians have about using guidelines, including concerns that they may be misapplied or abused, and the concern of "cookbook medicine".

A guideline was developed promoting a 2-day hospital stay for patients with chest pain who were considered to be at low-risk for complications and had a diagnosis of acute myocardial infarction dismissed.[1] A prospective, controlled interventional trial of this guideline to reduce hospital length of stay for patients admitted with chest pain showed the guideline decreased length of stay and hospital costs and did not have an adverse effect on patient morbidity, mortality, health status, or satisfaction. These reductions were achieved by improving physician compliance with the guideline from 50% during the control months to 69% during the interventional period.[2]

A recent study retrospectively analyzed the results of the prospective trial to determine the reasons why 31% of low-risk patients were not discharged at day 2 according to the guideline and the factors that may lead to a physician not to comply with a practice guideline.[3]

Seventy-nine patients classified as low-risk had a length of stay of 3 or more days. Of these 79 patients, 33 (42%) patients were misclassified during concurrent utilization review (23 patients falsely classified as low risk, 10 patients falsely classified as high risk). None of these patients died or had a substantial complication on follow-up.

Of the remaining 46 correctly classified low-risk patients, 7 (9%) patients had a clinical event within 48 hours that caused a reclassification to high-risk, and 11 (14%) patients were prevented from being discharged due to hospital/healthcare system inefficiencies, such as test scheduling problems, unavailable test results, or unavailable nursing home beds. No obvious reason for delayed discharge was found for 15 (19%) patients, but these patients were found to have a higher severity of illness than the low-risk patients discharged according to the guideline. In the remaining 13 patients (16%), physicians refused to follow the guideline recommendations.

This study shows that physician refusal to follow guidelines accounts for a small percentage (16%) of noncompliance. Other factors such as implementation issues, healthcare system inefficiencies, and severity of illness also contribute to deviation from guidelines. No guideline or pathway will have 100% sensitivity and specificity, and compliance should always be less than 100%. Guidelines should complement physician judgement rather than be a substitute for it.

References:
1. Weingarten S, et al. Am J Cardiol 1993;71:259-62.
2. Weingarten SR, et al. Ann Intern Med 1994;120:257-63.
3. Ellrodt AG, et al. Ann Intern Med 1995;122:277-82.

Erratum: Update 95-04

In PEC Update 95-04, the PEC provided an update on the Betaseron® program for DOD. The article indicated that CHAMPUS has clinical selection criteria for preapproval of Betaseron similar to the criteria for the DOD Betaseron® program. There are no *preapproval* requirements for Betaseron® obtained through CHAMPUS; however, the patient must meet the CHAMPUS clinical selection criteria to be reimbursed for the

Choking from Oral Syringes

Two types of syringes are used to administer oral medication: (1) standard hypodermic syringe without a needle, or (2) syringes specifically designed for oral administration of medication. Both types of syringes are supplied with caps that should be removed before the medication is drawn into the syringe or given to the patient.

Trying to administer oral medication through a syringe with the cap in place creates a potentially life-threatening situation. The cap could be blown off the end of the syringe into the patient's throat.

The FDA has received several reports of infants choking on plastic caps from syringes, and literature reports also describe syringe cap aspiration. In response to these reported events, the FDA recommends the following precautions:

- Remove and discard syringe caps before providing syringes for oral medication administration to patient care-givers. The American Academy of Pediatrics recommends providing syringe devices to primary care-givers that are specifically made for oral medications.
- Caution care-givers of your patients to discard caps from oral syringes that they purchase.
- Report any problems encountered with syringe caps to the FDA's MEDWATCH Program.

(Adapted from: FDA Medical Bulletin 1994;24(2):2.)

Antidepressant Update

As you are probably aware, fluoxetine (Prozac® - Lilly) has been suspended from the Tri-Service Formulary (TSF) as the sole antidepressive agent because of pricing issues related to the antidepressants. The PEC has published interim major depression guidelines for facilities to use while these pricing issues are resolved. These interim guidelines were mailed separately to medical treatment facilities in mid-February. If you did not receive a copy of the interim guidelines for the treatment of major depression, please contact the PEC.

For acquisition price information on the antidepressive agents, contact your local pharmaceutical manufacturer representative.

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Recommended Childhood Immunization Schedule

The following childhood immunization schedule was developed and endorsed by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians to ensure the earliest administration of vaccines. In the first year of life, 3 doses each of diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), *Haemophilus influenzae* type b (Hib) vaccine, and oral poliovirus vaccine (OPV) are recommended to be administered at ages 2, 4, and 6 months. The third dose of OPV may be administered through age 18 months. Children who receive *Haemophilus* b conjugate vaccine (Meningococcal Protein Conjugate) (PRP-OMP) at ages 2 and 4 months do not require a dose at age 6 months. The first dose of hepatitis B vaccine is recommended at birth, the second dose at age 2 months, and the third dose at age 6-18 months.

Vaccines recommended at age 12-15 months can be administered simultaneously during one visit or during two separate visits. The second dose of measles, mumps, and rubella vaccine (MMR) may be given when children start kindergarten or middle school. Diphtheria and tetanus toxoids (Td) is recommended at age 11-12 years, but may be given through age 14-16 years. If administered at age 11-12 years, healthcare providers can ensure that the child has received a second dose of MMR.

Recommended Childhood Immunization Schedule* - January 1995

Vaccine	Birth	2 months	4 months	6 months	12 months†	15 months	18 months	4-6 years	11-12 years	14-16 years
Hepatitis B‡	HB-1									
		HB-2		HB-3						
Diphtheria, Tetanus, Pertussis§		DTP	DTP	DTP	DTP or DTaP at ≥ 15 months			DTP or DTaP	Td	
H. influenzae type b‖		Hib	Hib	Hib	Hib					
Poliovirus		OPV	OPV	OPV				OPV		
Measles, Mumps, Rubella¶					MMR			MMR	or MMR	

* Recommended vaccines are listed under the routinely recommended ages. Shaded bars indicate range of acceptable ages for vaccination.

† Vaccines recommended in the second year of life (i.e., 12-15 months of age) may be given at either one or two visits.

‡ Infants born to hepatitis B surface antigen (HBsAg)-negative mothers should receive the second dose of hepatitis B vaccine between 1 and 4 months of age, provided at least 1 month has elapsed since receipt of the first dose. The third dose is recommended between 6 and 18 months of age. Infants born to HBsAg-positive mothers should receive immunoprophylaxis for hepatitis B with 0.5 mL Hepatitis B Immune Globulin (HBIG) within 12 hours of birth, and 0.5 mL of either Recombivax HB® (Merck Sharpe & Dohme) or Engerix-B® (SmithKline Beecham) at a separate site. In these infants, the second dose of vaccine is recommended at 1 month of age and the third dose at 6 months of age. All pregnant women should be screened for HBsAg during an early prenatal visit.

§ The fourth dose of diphtheria and tetanus toxoids and pertussis vaccine (DTP) may be administered as early as 12 months of age, provided at least 6 months have elapsed since the third dose of DTP. Combined DTP-Hib products may be used when these two vaccines are administered simultaneously. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is licensed for use for the fourth and/or fifth dose of DTP in children aged ≥ 15 months and may be preferred for these doses in children in this age group.

‖ Three *H. influenzae* type b conjugate vaccines are available for use in infants:
1.) oligosaccharide conjugate Hib vaccine (HbOC) (HibTITER® - Lederle-Praxis)
2.) polyribosylribitol phosphate-tetanus toxoid conjugate (PRP-T) (ActHIB™ - Connaught, and OmniHIB™ - SmithKline Beecham)
3.) *Haemophilus* b conjugate vaccine (Meningococcal Protein Conjugate) (PRP-OMP) (PedvaxHIB® - Merck Sharpe & Dohme)
Children who have received PRP-OMP at 2 and 4 months of age do not require a dose at 6 months of age. After primary infant Hib conjugate vaccine series is completed, any licensed Hib conjugate vaccine may be used as a booster at age 12-15 months.

¶ The second dose of measles-mumps-rubella vaccine should be administered EITHER at 4-6 years of age OR at 11-12 years of age.

Adapted from: Centers for Disease Control and Prevention. MMWR 1995;43:959-60.